UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/950,732	11/19/2010	Joffre B. BAKER	GHI-040/US	8330

80811 7590 12/05/2016

Genomic Health, Inc. / McNeill Baur PLLC
301 Penobscot Road
Redwood City, CA 94063

EXAMINER
BROWN, MINDY G

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
12/05/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

genomic_docketing@cardinal-ip.com
docketing@mcneillbaur.com
eofficeaction@appcoll.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOFFRE B. BAKER, MAUREEN T. CRONIN, FRANCOIS COLLIN and MEI-LAN LIU[1]

Appeal 2015-002690
Application 12/950,732
Technology Center 1600

Before JEFFREY N. FREDMAN, JOHN G. NEW and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to methods of predicting cancer recurrence, which have been rejected as being directed to non-statutory subject matter and nonenabled. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

---

[1] Appellants identify the Real Party in Interest as Genomic Health, Inc. (App. Br. 3.)

STATEMENT OF THE CASE

Appellants' "invention provides a set of genes, the expression levels of which are associated with a particular clinical outcome in cancer." (Spec. ¶ 7.) According to the Specification, "the clinical outcome could be a good or bad prognosis assuming the patient receives the standard of care. The clinical outcome may be defined by clinical endpoints, such as disease or recurrence free survival, metastasis free survival, overall survival, etc." (*Id.*)

The Specification further discloses

> the present invention concerns a method of predicting a clinical outcome of a cancer patient, comprising (a) obtaining an expression level of an expression product (e.g., an RNA transcript) of at least one prognostic gene [such as IL6ST] . . . (b) normalizing the expression level of the expression product of the at least one prognostic gene . . . and (c) calculating a risk score based on the normalized expression value, wherein increased expression of prognostic genes . . . are positively correlated with good prognosis.

(*Id.* at ¶ 9.)

Claims 1, 6, 19–22, 24, 26, and 28–30 are on appeal. Claim 1 is illustrative:

> 1. A method predicting whether a human patient diagnosed with breast cancer has an increased or decreased likelihood of cancer recurrence comprising:
>
> (a) quantitatively measuring a level of an mRNA transcript of IL6ST in a fixed, paraffin-embedded tissue sample obtained from a tumor of the patient;
>
> (b) normalizing the level of the mRNA transcript of IL6ST against one or more reference mRNA transcripts in the sample to obtain a normalized IL6ST expression level;
>
> (c) using a computer implemented program to compare the normalized IL6ST expression level to a statistical model-

> predicted relationship between normalized IL6ST expression level and likelihood of cancer recurrence determined from a population of patients with breast cancer and with known clinical outcome; and
>
> (d) generating a report comprising a prediction whether the patient has an increased or decreased likelihood of cancer recurrence.

(App. Br. 33 (Claims App'x).)

The claims stand rejected as follows:

Claims 1, 6, 19–22, 24, 26, and 28–30 under 35 U.S.C. § 101 as directed to non-statutory subject matter.

Claims 1, 6, 19–22, 24, 26, and 28–30 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

DISCUSSION

Patentable Subject Matter – 35 U.S.C. § 101

In analyzing patent eligibility under 35 U.S.C. § 101, the Supreme Court has set forth a "framework for distinguishing patents that claim [patent-ineligible] laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014). According to that framework, first "we determine whether the claims at issue are directed to one of those patent-ineligible concepts." *Id.* at 2355. "If so, we then ask, '[w]hat else is there in the claims before us?'" *Id.* (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1297 (2012).) To answer this second question,

> we consider the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application. [The Supreme Court has] described step two of this analysis as a search for an inventive concept — i.e., an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself.

Id. (internal citations and quotation marks omitted).

Appellants argue the patentability of the claims as a group. We select claim 1 as representative. 37 C.F.R. § 41.37(c)(1)(iv).

The Examiner rejected claim 1, finding that the claim is directed to a patent-ineligible law of nature. (Ans. 2.) According to the Examiner, "[t]he claims are drawn to a method for determining a likelihood of cancer recurrence of a human patient diagnosed with breast cancer" yet "[t]he correlation between the expression level of an RNA transcript and the patient's likelihood of cancer recurrence is considered a 'law of nature' in accordance with Mayo Collaborative Services v. Prometheus Laboratories, Inc." (*Id.*; *see also id.* at 12–15; *see also* Final Act. 3.)

The Examiner finds that "[t]he additional steps of measuring, normalizing, applying a statistical method, and generating a report are well understood steps that are routinely conducted to analyze an mRNA transcript . . . [and are] claimed at a high level of generality." (Final Act. 3; *see also* Ans. 3–4.) As the Examiner explains, "[a] claim that recites a law of nature or natural correlation, with additional steps that involve well-understood, routine, conventional activity previously engaged in by researchers in the field is not patent-eligible." (Ans. 4.) Thus, according to the Examiner,

"considered as a whole, the steps taken together amount to no more than recognizing the law of nature itself." (Final Act. 3.)

We agree with, and adopt, the Examiner's findings and conclusion that claim 1 is ineligible for patenting under § 101. (Ans. 2–5 and 12–15; Final Act. 2–3.) Analyzing claim 1 according to the *Alice/Mayo* framework, we agree with the Examiner that claim 1 is directed to a law of nature or natural phenomenon that is a correlation or association between an expression product (mRNA of IL6ST) and cancer risk. With respect to the claim elements individually and as an ordered combination — step two of the *Alice/Mayo* framework — the Examiner finds the steps of measuring, normalizing, comparing, and generating a report are conventional and routine steps previously engaged in by those in the field. *See* Mayo, 132 S.Ct. at 1298 ("well-understood, routine, conventional activity previously engaged in by scientists who work in the field . . . is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such law.") Appellants have not persuasively shown otherwise.

We address below Appellants' arguments.

Appellants argue "the instant claims are not directed to a natural phenomenon . . . [and instead] recite *a statistical model-predicted relationship between normalized IL6ST expression level or a normalized IL6ST amplicon level and likelihood of cancer recurrence*." (App. Br. 8.) As such, Appellants contend, the claims are "NOT a product of nature, but [] rather a product of human ingenuity and human intervention." (*Id.* at 9.)

This argument is unpersuasive. At its core, claim 1 is drawn to a natural phenomenon or law of nature — the correlation between expression

levels of an mRNA of IL6ST and a risk of cancer recurrence. We are not persuaded that the recitation of a statistical model does significantly more than exploit and inform a relevant audience about the correlation itself. *See Mayo*, 132 S. Ct. at 1297 ("The process that each claim recites tells doctors interested in the subject about the correlations that the researchers discovered."); *Digitech Image Techs. LLC v. Elecs. For Imaging, Inc.*, 758 F.3d 1344, 1351 (Fed. Cir. 2014) ("Without additional limitations, a process that employs mathematical algorithms to manipulate existing information to generate additional information is not patent eligible.")

Appellants further argue "prediction of the likelihood of an outcome using a statistical model is not a natural phenomenon" and instead "takes human action and human ingenuity to make such a prediction." (App. Br. 9.) This argument fails to persuade us that claim 1 is drawn to patent-eligible subject matter. On this point, we turn to the Supreme Court's guidance in *Mayo*. The claims in *Mayo* recited a "method of optimizing therapeutic efficacy for treatment" requiring, *inter alia*, "administering" and "determining" steps that "take[] human action" and were "not themselves natural laws." *Mayo*, 132 S.Ct. at 1295, 1297. The claims further required that the outcome of the "determining" step would indicate [to the doctor] a need to either increase or decrease the amount of drug administered to a patient. *Id.* Notwithstanding these claim elements requiring human intervention, the Court held that the claims were drawn to patent-ineligible "laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of thiopurine drug will prove ineffective or cause harm." *Id.* at 1296.

Claim 1 is analogous to the patent-ineligible claims in *Mayo*. Although the "statistical model" and "prediction" recited in Appellants' claim 1 may involve human (or computer) intervention, we are not persuaded those elements transform claim 1 into a patentable application of the natural law or phenomenon.[2] *Id.* at 1295–96; *see also Alice*, 134 S. Ct. 2358 ("the mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention.")

Appellants further argue that, even if the claims recite a law of nature or natural phenomenon, the claims as a whole recite something "significantly different." (App. Br. 9.) In this respect, Appellants contend claim 1 is meaningfully limited, and thus does not foreclose others from using the natural phenomenon, because the claims relate to a single type of cancer, analyte, gene, and sample type. (*Id.* at 10–11.) Appellants further contend "the pending claims do not claim a known, proven, direct mechanistic connection between a biological marker and a particular disease" but rather "a statistical correlation between one or more physiochemical characteristics of specific biomarkers and the underlying disease." (*Id.* at 11.) In other words, Appellants argue, "the pending claims

---

[2] The Examiner found that "Applicant has not recited [in claim 1] a specific statistical model." (Final Act. 3.) Appellants acknowledge as much, but contend "one of ordinary skill in the art reading the claims in light of the specification would understand the statistical methods encompassed," and Appellants cite paragraph 133 of the Specification as an example. (App. Br. 8.) Claim 1 broadly recites "a statistical model-predicted relationship" and we decline to read limitations from the example cited by Appellants into the claims. *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

are drawn to a clinically useful statistical approximation of a biological reality identified by scientists, not simply to a law of nature." (*Id.*)

These arguments are unpersuasive. With respect to Appellants' contention that the claims do not foreclose all uses of a natural phenomenon, the Federal Circuit's analysis in *Ariosa* is instructive. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (2015), *cert. denied* 579 U.S. __ (2016). In *Ariosa*, Appellants argued "the particular application of the natural phenomena that the [] patent claims embody are narrow and specific" and thus did not "preclude alternative methods [of using cffDNA] in the same field." *Ariosa*, 788 F.3d at 1378. The Federal Circuit nevertheless held that "the absence of complete preemption does not demonstrate patent eligibility" and noted that "[t]he Supreme Court cases [] have not distinguished among different laws of nature or natural phenomenon according to whether or not the principles they embody are sufficiently narrow." *Id.* at 1379. The Federal Circuit further held that "[w]here a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework, . . . preemption concerns are fully addressed and made moot." *Id.*

Appellants' argument here that the claims are narrow and not wholly preemptive fares no better than the similar, but unsuccessful, argument in *Ariosa*. As noted above, under the *Alice/Mayo* framework, Appellants' claims are drawn to a patent ineligible natural phenomenon, and Appellants have not persuasively shown that the Examiner erred in finding the claim elements, individually and in combination, are conventional steps previously employed by skilled persons that do not impart an inventive concept. (Ans.

2–5; *See*, *e.g.*, Spec. ¶ 64 ("The present disclosure provides methods that employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, and biochemistry, which are within the skill of the art. Such techniques are explained fully in the literature.") Appellants' argument concerning preempting or foreclosing others from access to the claimed natural phenomenon or law of nature is thus unpersuasive.

Appellants' contention that they are claiming a "statistical correlation" and not "a known, proven, direct mechanistic connection" between mRNA expression levels and risk of breast cancer recurrence also fails to persuade us that claim 1 is patentable under § 101. According to Appellants, "as any statistician will tell you, '*correlation* does not imply *causation*.'" (App. Br. 11.) Yet, whether Appellants discovered a cause or a correlation between expression levels and cancer risk, the discovery remains drawn to a patent-ineligible natural phenomenon or law of nature, just as the natural laws at issue in Mayo were "*correlations* between metabolite levels and likely harm or ineffectiveness." *Mayo*, 132 S. Ct. at 1295 (emphasis added). We are also unpersuaded on the present record that reducing a naturally-occurring correlation to a statistical model, or expressing as a statistical relationship, provides a sufficient inventive concept. *Cf. Alice*, 134 S. Ct. 2356–57 ("One of the claims in *Bilski* reduced hedging to a mathematical formula, but the Court in did not assign any special significance to that fact, much less the sort of talismanic significance petitioner claims."); *see also Digitech*, 758 F.3d at 1351.

Inasmuch as Appellants also address the § 101 rejection based on the 2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena and/or Natural Products ("the 2014 Guidance") (*see, e.g.*, App. Br. 12–14; Reply Br. 2–7), the 2014 Guidance is encompassed by analysis under the *Alice/Mayo* framework. And, for the reasons discussed above, Appellants' arguments concerning the patentability of claim 1 under the 2014 Guidance are unpersuasive.

We conclude the preponderance of the evidence supports the Examiner's determination that claim 1 is unpatentable under 35 U.S.C. § 101. Claims 6, 19–22, 24, 26, and 28–30 were not argued separately and thus fall with claim 1.

Enablement – 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1, 6, 19–22, 24, 26, and 28–30 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The issue with respect to this rejection is: has the Examiner established by a preponderance of the evidence that the Specification does not enable the claimed invention?

Principles of Law

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561–62 (Fed. Cir. 1993). "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Id.* at 1561.

> Factors to be considered in determining whether a disclosure would require undue experimentation … include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Findings of Fact/Wands Factors

Breadth of Claims and Nature of the Invention

1. The Examiner finds "[t]he claims are broadly drawn to a method for determining a likelihood of cancer recurrence of a human patient diagnosed with breast cancer." (Ans. 6.) The Examiner further finds that specific "aspects considered broad are: (i) the use of an RNA transcript of IL6ST, and (ii) the range of level of increase of the RNA transcript or expression product thereof." (*Id.* at 7–8.)

2. The Examiner finds "the nature of [Appellants'] invention is within the broad genera of using a gene expression level to predict breast cancer patient prognosis." (Ans. 7.)

Predictability and State of the Art

3. The Examiner finds that "[w]ith respect to the correlation between an[] increased level of an RNA transcript of IL6ST and a 'good prognosis', the art teaches that an increased level of an RNA transcript of IL6ST is

associated with invasive, metastatic breast tumors indicative of a poor prognosis." (Ans. 8 (citing Garcia-Tuñón[3]).) According to the Examiner,

> from the nature of the invention and the state of the art, the Artisan would not reasonably predict that the increase of RNA transcript level of IL6ST would be indicative of a reduced cancer recurrence, as broadly claimed by the rejected claims, and in fact the prior art teaches the increased level of an RNA transcript of IL6ST is indicative of a "poor prognosis."

(Ans. 9.)

4. Garcia-Tuñón discloses "[i]n invasive breast tumours, the percentage of cases showing immunoreactivity for IL-6, gp130 and IL-6Rα was much higher (from 74.0% to 92% of cases) than in non-malignant lesions (23.0–53.8%), and the intensity of expression was two to three times higher." (Garcia-Tuñón 87.) The Examiner thus finds that Garcia-Tuñón "teach a gp130 (gp130 is another name for IL6ST) expression level increase of 74-92% in invasive breast tumors . . . [and] describe[s] only a weak expression of gp130 is observed in benign lesions." (Ans. 8.)

5. The Examiner finds that "Crichton [] observed that the IL-6 receptor (IL6ST) was not observed in tissue surrounding a tumor, was only observed in the tumor tissue, and that IL-6 and the IL-6 receptor promote tumor progression." (Ans. 8 (citing Crichton[4]).) According to the

---

[3] Garcia-Tuñón et al., *IL-6, its receptors and its relationship with bcl-2 and bax proteins in infiltrating an in situ human breast carcinoma*, 47 HISTOPATHOLOGY 82–89 (2005).

[4] Crichton et al., *Expression of transcripts of interleukin-6 and related cytokines by human breast tumors, breast cancer cells, and adipose stromal cells*, 118 MOLECULAR AND CELLULAR ENDOCRINOLOGY 215–220 (1996).

Examiner, "[a]s evidenced by Karczewska . . . IL-6 is known to be a promoting or inhibitory factor in various types of tumors (page 2062) further demonstrating the unpredictability of making any prognosis by examining the levels of components of this [gp130 signaling] pathway." (Ans. 17–18 (citing Karczewska[5]).)

6. The Examiner finds that "Gao et al. detected a reduction of IL-6 by RNA interference leading to a decrease in tumorgenesis . . . [and] further stat[ed] that IL-6 leads to activation of the gp130 signaling pathway." (Ans. 8 (citing Gao[6]).) Thus, the Examiner finds, "when the IL-6 expression is decreased it does not activate the gp130 signaling pathway and tumorgenesis is decreased. The prior art indicates that the activation of the IL-6/gp130 pathway leads to an increase in tumorgenesis." (*Id.* at 9)

7. The Examiner finds that, "[b]ecause the claims encompass detecting any level . . . of gene expression in a sample from an individual . . . it is relevant to point out the unpredictability associated with gene expression in any individual." (Ans. 9.) Also, the Examiner finds "the claims broadly encompass determining that an RNA transcript level is 'increased', with no standard or references with regard to what would be considered, for example, a normal level." (*Id.* (citing Cheung[7]).)

---

[5] Karczewska et al., *Expression of Interleukin-6, Interleukin-6 Receptor, and Glycoprotein 130 Correlates with Good Prognoses for Patients with Breast Carcinoma*, 88:9 CANCER 2061–2071 (2000).
[6] Gao et al., *Mutations in the EGFR kinase domain mediate STAT3 activation via IL-6 production in human lung adenocarcinomas*, 117:12 JOURNAL OF CLINICAL INVESTIGATION 3846–3856 (2007).
[7] Cheung et al., *Natural variation in human gene expression assessed in lymphoblastoid cells*, 33 NATURE GENETICS 422–425 (2003).

Amount of Direction/Guidance and Presence of Working Examples

8. The Specification discloses examples including "a study [] of breast cancer tumor samples obtained from 136 patients with breast cancer ('Providence study')" and an example involving "samples obtained from 78 evaluable cases from a Phase II breast cancer study conducted at Rush University Medical Center" ("Rush study"). (Spec. ¶¶ 130–132 and 134–135.)

9. The Examiner finds that Appellants' Specification provides only "generic guidance" with respect to the examples. (Ans. 9–10.) For instance, the Examiner finds the Specification provides "a general reference to an increase or decrease in RNA transcript after normalization" and "a reference to a correlation between an increased RNA transcript level and a 'good prognosis' . . . ." (*Id.* at 10.) The Examiner further finds that

> [w]hile "prognosis" is defined [0024] and "good prognosis . . . may be an expectation of no recurrences or metastasis" the working example does not provide any patient data to define "cancer recurrence" in the invention. There is no data to suggest a time period for cancer recurrence or any patient data for that matter to indicate the correlation between IL6ST expression levels and patient outcome. . . . A cancer-related event is not defined and no patient data is provided to indicate how this term is applied in a clinical context. Furthermore, the Providence Study, Providence Phase II Study, and a phase II breast cancer study are referenced without providing any information about the patient outcome and how that outcome relates to cancer recurrence. . . . [In] Table 1 the gene IL6ST is listed as having a negative z score without any reference to individual patient scores or a comparison to the patient's outcome. Therefore, the specification does not reasonably demonstrate that a specific patient's increase in RNA transcript level is predictive of a reduction in cancer recurrence in breast cancer patients.

(*Id.* at 10–11.)

Amount of Experimentation Necessary

10. The Examiner finds "a large and prohibitive amount of experimentation [would be] required to make and use the claimed invention in the full scope as encompassed by the claims." (*Id.* at 11.) For example, according to the Examiner, "[o]ne would have to establish that any level of increase in IL6ST RNA transcript that will result in a negative z score, is in fact indicative that a patient has a reduced likelihood of cancer recurrence" and "one would have to establish what the correlation [is] between reduced 'cancer recurrence' and an increased level [of] IL6ST RNA transcript through clinical trials that detail patient outcome." (*Id.*)

Analysis

Appellants argue the patentability of the claims subject to the enablement rejection as a group. We select claim 1 as representative.

Based on the findings concerning the *Wands* factors as noted above, the Examiner concludes there "would be an undue amount of experimentation required to make and use the invention" and thus claim 1 is not enabled by the Specification. (Ans. 11; *see also* Ans. 6–10 and 15–21.)

Appellants argue the Examiner has not sufficiently explained why the Examiner considers claim 1 broad. (App. Br. 17.) According to Appellants, claim 1 is, in fact, "narrowly drawn to embodiments measuring transcript expression levels of a single gene encoding IL6ST . . ., normalizing those expression levels to account for variability, . . . and computer-based

implementation of a statistical model to predict . . . an increased or reduced likelihood of breast cancer recurrence." (App. Br. 23.)

This argument is unpersuasive. We agree with the Examiner that claim 1 is broad. (FF 1–2.) Among other things, claim 1 recites "quantitatively measuring" and "normalizing" a level of an mRNA transcript of IL6ST. But the claim provides no range or other limitation of the level, nor does the claim include limitations specifying any particular level or range that correlates to an increased or decreased likelihood of cancer recurrence. Insofar as the correlation is embodied in the "statistical-model predicted relationship," that claim element is itself broadly phrased. The Specification suggests that *increased* expression of an expression product of IL6ST is positively correlated with a "good prognosis," but claim 1 is broader than even this expansive disclosure. (*See, e.g.*, Spec. ¶ 9.) Moreover, although Appellants defined terms like "prognosis" and "recurrence," those definitions are themselves broad. (*See, e.g.*, *id.* at ¶ 38 (defining recurrence as "local or distant (metastasis) recurrence of cancer.")

Appellants contend that, contrary to the Examiner's findings, "the art is not unpredictable." (App. Br. 23–29; Reply Br. 10–11) Appellants argue the "references [cited by the Examiner] are not relevant to assessing patentability of the claimed invention, and they do not demonstrate that the art is not [sic] unpredictable." (Reply Br. 11.)

More specifically, Appellants argue "Crichton does not disclose measuring expression IL6ST . . . but only cytokines of the IL-6 family and IL-6 receptor alpha" and thus is irrelevant to expression of IL-6Rβ/gp130/IL6ST. (App. Br. 24.) Appellants argue "Gao is similarly

irrelevant" because "it discloses only measuring expression of some components of the IL-6 signaling pathway in human lung cancer-derived cell lines, not in breast cancers." (*Id.*) Appellants contend Garcia-Tuñón does not reflect the state of the art because it was published in 2005 — more than four years before the alleged priority date of the present application. (App. Br. 25.) Appellants also contend Garcia-Tuñón does not show that the art is unpredictable because it measured IL6ST protein levels, not the level of IL6ST mRNA. (*Id.* at 25–26.) According to Appellants, protein levels do not necessarily correlate with RNA expression levels (*id.* at 26) as shown in literature (*see, e.g., id.* at 27 ("one skilled in the art cannot predict whether expression levels of a particular RNA and protein will correlate without experimental verification") (citing Hanash[8]).) Appellants argue Cheung does not render the art unpredictable because, even if Cheung discloses natural variation in gene expression among individuals, the claims include a "normalizing" step "because it is necessary to account for such variability." (App. Br. 28.)

Although Appellants' contentions raise questions concerning how much weight, if any, to assign each of the references cited by the Examiner, the preponderance of the evidence of record supports the Examiner's determination that the art was unpredictable. Indeed, considered together, the references including at least Garcia-Tuñón, Crichton, and Gao suggest unpredictability existed concerning the associations between cancer and IL-6

---

[8] Hanash et al., *Operomics: Integrated genomic and proteomic profiling of cells and tissues*, 1:1 BRIEFINGS IN FUNCTIONAL GENOMICS AND PROTEOMICS 10–22 (2002).

and its receptors (including gp130/IL6ST). (FF 3–6.) As the Examiner noted, at least Garcia-Tuñón arrives at a conclusion concerning this association that is seemingly at odds with Appellants' discovery. (Ans. 19.) Appellants seek to diminish Garcia-Tuñón because it examined IL6ST protein levels not mRNA levels; we note, however, that Appellants' Specification defines "gene product" and "expression product" as including, for example, both mRNA and "polypeptide translation products." (Spec. ¶ 34.) And, as the Examiner points out, Appellants have "not provided evidence that the mRNA expression levels of IL6ST do not correspond with protein expression." (Ans. 20.) Appellants also question Garcia-Tuñón's relevance because it was published four years before Appellants' filing. But Appellants submitted no evidence reflecting a material change in the state of the art in the years between 2004 and 2009. Moreover, in the face of the Examiner's evidence of unpredictability in the art, and even assuming the artisan is highly skilled (App. Br. 23), Appellants provided no countervailing argument or evidence demonstrating that the art was *predictable*.

Regarding the amount of guidance or direction provided by the inventors, including working examples, Appellants contend "[t]he specification discloses that IL6ST is a prognostic gene, increased expression of which positively correlates with good prognosis, a finding that is supported by data disclosed in the Examples and presented in the accompanying Tables." (App. Br. 20–21.) In response to the Examiner's findings on the absence of specific data about levels of IL6ST mRNA transcript and patient outcomes, Appellants contend "[o]ne of ordinary skill . . . would understand that information about patient outcome is taken into

account while performing the statistical analysis described in the Examples." (App. Br. 29; *see also* Reply Br. 12.) Appellants argue "the skilled artisan would understand the standard time periods over which cancer recurrence or survival is measured" and also "the specification defines the relevant terms, including 'long-term survival[,]' 'good prognosis[,]' and 'recurrence-free survival[.]'" (App. Br. 29; *see also* Reply Br. 12–13.)

We have considered Appellants' arguments and the cited data from the Specification but it does not outweigh other evidence favoring the Examiner's determination that the full scope of claim 1 is not enabled.[9] The detail concerning the Examples provided in the Specification is wanting: as the Examiner noted, "Applicant has not provided patient data in regards to clinical outcome regarding cancer recurrence" and "has provided no measure to indicate how 'cancer recurrence' is measured or if it in fact was measured." (Ans. 17; FF 8–9.) Given the breadth of the claims, including what constitutes a "known clinical outcome" and "an increased or decreased likelihood of cancer occurrence," the Examiner was reasonable in pointing out the missing data. Appellants argue the patient outcomes are accounted for in the statistical analysis and would be understood by skilled persons, but do not support that argument with sufficient persuasive evidence. *See In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997) (argument by counsel cannot take the place of evidence).

---

[9] Appellants provide no citation or persuasive argument on appeal concerning the Mar. 15, 2013 declaration of co-inventor Mei-Lan Liu, Ph.D. ("Liu Declaration.") In any event, the details in the Liu Declaration are not included in the Specification and so were not part of an enabling disclosure.

Finally, with respect to the amount of experimentation required, Appellants argue the Examiner essentially asserts that the skilled person "would have to repeat the analysis" in the Specification "without providing a shred of evidence giving any reason whatsoever to doubt the objective truth of the disclosure." (App. Br. 31.) We are unpersuaded. As the Examiner explained, "to make and use the claimed invention, one of ordinary skill . . . would necessarily need information about the outcome of the patients from which the level of IL6ST was determined" and, because this information is absent in the Specification, "[a] study covering an unidentified number of years would need to be undertaken to determine a cancer recurrence in those patients." (Ans. 21; FF 10.)

Upon considering and weighing all the *Wands* factors, the preponderance of the evidence supports the Examiner's conclusion that undue experimentation would be required to practice the full scope of claim 1. Claims 6, 19–22, 24, 26, and 28–30 were not argued separately and thus fall with claim 1.

SUMMARY

We affirm the rejection of claims 1, 6, 19–22, 24, 26, and 28–30 under 35 U.S.C. § 101 as directed to non-statutory subject matter.

We also affirm the rejection of claims 1, 6, 19–22, 24, 26, and 28–30 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED